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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,799	12/20/2001	Beuford Arlie Bogue	24720	4794

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,799	BOGUE, BEUFORD ARLIE	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,21-28,30-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18, 21-28, 30-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and remarks all dated 5-11-06 is acknowledged.

Claims 18, 21-28, 30-36 and 38 are pending in the instant application.

The following is a new rejection:

Claim Rejections - 35 USC § 112

1. Claims 18, 21-28, 30-36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 18 recite 'if dissolution than pure unprocessed drug", which is an incomplete and unclear limitation. It is not clear from the expression as to what is the consequence of "if dissolution" and what is greater than "if dissolution". Is it the dissolution of drug or surfactant or both? A clarification is requested.

Instant claim 23 recites that the surfactant is an organic excipient. However claim 24, dependent from claim 23, lists a number of excipients including organic solvents, phosphates, non-crystalline cellulose etc., which are not emulsifiers by nature. For instance, the claimed organic solvents include ethanol, isopropanol, which are not used as surfactants and are used as solubilizers instead. Similarly, the term phosphates relates to numerous compounds all of which are not necessarily surfactants. A clarification and correction is requested.

2. Claim 18, 21-28, 30-36 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving the solubility of dimenhydrinate by processing dimenhydrinate into Pluronic surfactant, does not reasonably provide enablement for improving the solubility of or all the drugs with any surfactant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims are directed to a method of improving solubility of a drug by processing the drug into a surfactant-coated particulate form comprising the steps of

1. Melting the drug into a molten surfactant miscible with the drug,

2. Heating the mixtures to above the melting temperature and below the drug's decomposition temperature until a clear mixture is formed,

3. Cooling the mixture to approximately room temperature while continuously mixing under high shear to maximize the precipitation of the particles.

Instant claims broadly recite, "improving drug solubility" and 'surfactant", thus encompassing innumerable drugs and surfactants. The claimed "drugs" according to the specification (as well as claim 22) include several classes of drug. It is generally known in the art that drug dissolution depends on the nature of the drugs i.e., water soluble and insoluble drugs have different dissolution patterns upon administration. Instant specification describes that to increase the solubility the drug is first added to a molten surfactant, melting the mixture and cooling under high shear. Instant specification describes the method of improving the solubility of the drug dimenhydrinate with a

surfactant Pluronic. The process of improving the solubility described in the specification only employs grinding the drug-surfactant melt in a mortar and pestle (high shear) so as to form the claimed coated particles. However, instant specification does not provide any guidance if this method of melting and grinding in a mortar and pestle results in a surfactant coated microparticles for all the drugs and with a all the surfactants. This is further supported by applicants' description that in order to obtain sufficient cooling, such that the crystals do not grow on the surfactant, cooling should be performed under high shear (0064-0065). In the absence of what constitutes a high shear –is it simple grinding or a high vortexing or centrifuging at high speeds such as 3000 rpm etc., one cannot extrapolate the method practiced with one drug (in the specification) to all possible drugs and surfactants because not all the drugs and surfactants have the same melting points, and therefore the mixtures have different eutectic temperatures and also the cooling rates vary with drugs and surfactants employed. The specification admits that for stability reasons, the surfactant should have a melting point above room temperature and preferably, above 40 degrees C (0061). Thus, the final outcome of the claimed method i.e., drug with improved solubility depends several factors such as on the type or solubility of the drug, melting point of the surfactant, the high shear employed (such that the cooling occurs properly), all of which are specific depending on the drug and surfactant and the eutectic mixture. In the absence of the guidance as to how to optimize the above conditions such that the solubility of any kind of drug can be improved and with the exemplification just one type of drug and one type of surfactant, one of an ordinary skill in the art at the time of the instant invention was made would not

be able to practice the claimed method of improving the drug solubility with any drug, any surfactant.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

3. Claims 18, 21-28, 30-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/40943 (WO).

WO teaches solubilizing delivery systems for poorly soluble drugs and the process of solubilizing the drugs so as to enhance the solubility of the drugs. The process of WO comprises processing of particles of at least one active agent and at least one solubilizing agent (surfactant) at temperatures below the melting points of both drug and surfactant (eutectic temperature). The processing further involves applying shear forces after melting the drug and surfactant at the eutectic temperatures (page 2, lines 20-31; page 3, lines 6-16 and lines 26-30 & page 4, lines 1-3), resulting in crystalline drug particles coated with the surfactant. Thus, the process of WO reads on the instant claimed method steps. With respect to the melting points, instant claims require melting a mixture of drug and surfactant at a temperature above the melting point of the mixture, such that a clear mixture is formed. A review of the specification on pages 20 (lines 1-5) and 22-23 reveals that while a clear mixture results in micro and nano-crystals claimed, it is also stated that sometimes the inventive method also results in the formation of solid. Thus, it is not necessary that the claimed method always render a clear mixture. Further, instant figure 1 shows that the eutectic point of the drug

and surfactant shows a melting point below the individual melting points of drug and surfactant. In this regard, WO also teaches processing drug and surfactant below their individual melting points. Even though instant claims recite "above the mixture's melting point", the said melting point of the mixture is still below their individual melting points of the drug and surfactant and thus meets the instant requirement. Accordingly, absent any unexpected results with the claimed " melting the mixture above the mixture's melting point", it would have been obviuous for one of an ordinary skill in the art at the time of the instant invention to use the melting temperatures suggested by WO and still prepare micro or nano-crystalline particulate drug substances.

WO teaches the claimed drugs and surfactants suitable for the invention on page 5 and 6; and their amounts on page 4, lines 17-25, all of which are claimed in the instant application. WO teaches employing micronized drug (example I) for the processing and hence meet claim 21. With respect to the particle size, WO states that the particle size before processing is less than 10 microns or even preferably less than 6 microns (page 5, lines 16-18) and absent showing evidence to the contrary, the process of applying high shear (of WO), yields crystalline particles of much smaller size. The claimed matrix, miscibility and the absence of bonding between the drug and the surfactant is inherent to the composition of WO because the drug and surfactant are processed inexactly the same way as described in the instant specification. WO fails to specifically teach the carrier, diluent, binder etc., for the drug. However, WO suggests mixing the surfactant coated drug particles (after processing) with various pharmaceutical ingredients such as binders, flow control agents, fillers, sweeteners etc. Accordingly, it would have been

within the scope of a skilled artisan at the time of the instant invention to include any suitable pharmaceutical additive such as a binder or sweetener depending the desired pharmaceutical effect.

Response to Arguments

Applicant's arguments filed 5-11-06 have been fully considered but they are not persuasive.

Applicants argue that the process of WO combines drug and surfactant at low temperatures, in the presence of forces sufficient to produce active/solubilizer eutectic and that WO does not teach the claimed "melting" of the drug in a molten surfactant. It is argued that WO does not teach a clear solution is formed and in fact teaches away as cited on page 4, lines 11-16. Applicants' arguments are not persuasive because, it is admitted that WO teaches improving solubility of a poorly soluble drug by a process of surfactant coating drug particles. Instant claims differ from that of WO, only with respect to the "adding drug to a molten surfactant and melting of the drug and surfactant at a temperature below the drugs' decomposition temperature". While it is true that WO does not suggest heating too far above a point at which the eutectic alloy forms, WO teaches away from a super saturated solution of drug in the surfactant. Applicants have not established the criticality of the claimed step of melting and the temperature limitation. In this regard, even though instant claims recite "above the mixture's melting point", the said melting point of the mixture is still below their individual melting points of the drug and surfactant and thus meets the instant requirement. Accordingly, absent any

unexpected results with the claimed " melting the mixture above the mixture's melting point", it would have been obviuous for one of an ordinary skill in the art at the time of the instant invention to use the melting temperatures suggested by WO and still prepare micro or nano-crystalline particulate drug substances. Applicants' argument that the melting point of WO is preferably below the eutectic temperature is not persuasive because the teachings of prior art are not limited to preferred embodiments and instead should be considered as a whole and the previous paragraph clearly explains how the melting temperatures of WO meet the instant claimed. As also admitted by applicants, WO clearly suggests the importance of the melting temperature and cooling step, in obtaining the desired crystals, which is also a function of active agent (teachings of WO cited by applicants in the remarks).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615
July 23, 2006